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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

LY, CHEYNE D

ART UNIT PAPER NUMBER

1631

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/917,800

Applicant(s)

MENDRICK ET AL.

Examiner

Cheyne D. Ly

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 January 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 92-129 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 92-129 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1/27/2005</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 27, 2005 has been entered.
2. The cancellation of claims 1-91 and the addition of claims 92-129 have been acknowledged.
3. The rejections in the previous Office Action have been withdrawn as necessitated by the claim amendments.
4. The restriction requirement, mailed February 05, 2003, has been withdrawn.
5. Claims 92-129 are examined on the merits.

OBJECTIONS

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (Page 23, Line 30). Applicant(s) is/are required to delete the embedded hyperlink and/or other form of browser-executable code, or inactivate the hyperlink. See MPEP § 608.01.
7. On page 43, Applicant refers to the "U.S. Provisional Application 60/_____" wherein the Application number is incomplete.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 109 and 128 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 109 and 108 recite the limitation of "the genes in Tables 3A-3S are rat genes" which causes said claims to be vague and indefinite because Table 1 comprises sequences from *R. norvegicus* (rat), *M. musculus* (mouse), and unknown. Applicant discloses the data in Tables 3A-3S are directed to the sequences listed in Table 1. Table 1 comprises sequences from *R. norvegicus* (rat), *M. musculus* (mouse), and unknown. Therefore, it is not clear whether the genes in Tables 3A-3S are exclusively rat, or a combination of rat, mouse, and other species. Clarification of the metes and bounds is required.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

LACK OF ENABLEMENT

12. Claims 92-129 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

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13. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

14. It is noted that the instant specification discloses that microarray samples are prepared from frozen tissue (page 39, lines 12-14). Further, the tissue types collected are liver, heart, kidneys, testes, and brain (pages 38-39). The data generated from the microarray are disclosed in Tables 3A-3S. Therefore, the data in said tables have been reasonably construed to comprise gene expression profiles from liver, heart, kidneys, testes, and brain. One of skill in the art would not know how to predictably practice the method of predicting hepatotoxicity or liver toxicity without undue experimentation as discussed below.

15. For example, claims 92 and 111 are respectively directed to the method of predicting hepatotoxicity or liver toxicity. The method requires the preparation of a gene expression profile from a liver tissue or liver cell sample exposed to a test compound. The database has been

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populated with data generated from liver, heart, kidneys, testes, and brain harvested from Sprague-Dawley rats exposed to a known toxin. The claimed method requires the comparison of a gene expression profile from a liver tissue or liver cell sample exposed to a test compound to said database. Because the data in the database is from liver, heart, kidneys, testes, and brain, the method would not result in predicting a toxic condition specific to the liver as claimed.

Therefore, one of skill in the art would not know how to predictably use the claimed method specific to hepatotoxicity or liver toxicity by comparing expression profile generated from a liver tissue or liver cell sample exposed to a test compound to data in said database. One of skill in the art would require undue experimentation to be able to predict hepatotoxicity or liver toxicity when the comparison is performed with a database comprising expression data from liver, heart, kidneys, testes, and brain.

16. Further, it is noted that the data in Tables 3A-3S comprises the LDA from the toxicity group and non-toxicity group. However, said data does not provide enablement support for the claimed method. The specification does not disclose whether the LDA of the toxicity group and non-toxicity group is derived from the comparison between expression profiles between a liver sample and heart, kidneys, testes, or brain, individually or as a group. Without the disclosure that differential expression is specific to liver toxicology, but not other tissues, one of skill in the art would not be able to predictably practice the method as claimed. Therefore, one of skill in the art would not know how to predictably practice the claimed method specific for liver toxicity without undue experimentation.

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17. Applicant discloses Tables 3A-3S comprises gene expression profiles of sequences from GenBank listed in the Table 1. Table 1 comprises the identities of the metabolic pathways in which the genes function, the gene names if known, and the unique cluster. It is noted that Table 1 does not comprise the identities of the metabolic pathways in which genes function for all the genes in Table 1. Further, Applicant does not provide any disclosure as to whether the genes listed are specific for the metabolic pathways in the liver, or said genes function specifically in the liver that are involved in hepatotoxicity. For example, the sequences denoted with GLGC IDs 11426 to 11504 do not have data corresponding to pathways in general or corresponding to pathways that have been implicated in hepatotoxicity. Therefore, one of skill in the art would not know how to predictably practice the claimed method specific for liver toxicity without undue experimentation.

18. Specific to claims 105 and 124, said claims recite specific disease pathologies that are predicted with the claimed method. Further, Table 1, column 2, provides comparison codes listed in Table 2. However, Applicant does not disclose whether the comparison is performed with normal liver tissue and liver tissues having the respective liver disease pathologies. For example, Table 3D comprises data directed to necrosis with or without fatty liver wherein the toxic group is compared to non-toxic group. It is not apparently clear that the differential expression listed in Table 3D resulted from the comparison of data from liver having the specific pathology with data from normal liver. Therefore, one of skill in the art would not know how to predictably practice the claimed method specific for liver toxicity as directed to the specific disease pathologies without undue experimentation.

LACK OF WRITTEN DESCRIPTION

19. Claims 92-129 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

20. The specification discloses Tables 3A-3S, which recite GLGC IDs corresponding to sequences as denoted by Sequence IDs in Table 1, column 3. Claims 92-129 encompass "the genes in any one of Tables 3A-3S." With the exception of the SEQ ID Nos. disclosed in Table 1, none of the sequences, as encompassed by the limitation of the genes, meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

21. With the exception of the sequences denoted by SEQ ID Nos. in Table 1, the skilled artisan cannot envision the detailed chemical structure of the sequences encompassed the genes, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and

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Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In *Fiddes v. Baird*, 30

USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that: ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

22. Therefore, only the sequences denoted by SEQ ID NOs. in Table 1, but not the full breadth of the claims 92-129 meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

23. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Specifically, the instant specification recites GenBank IDs (Table 1) without disclosing the sequences corresponding to said IDs. Further, the sequences applicant attempting to incorporate in the specification are considered to be essential material for the claimed method. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material

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is relied upon to overcome any objection, rejection, or other requirement imposed by the Office.

The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

CLAIM REJECTIONS - 35 USC § 102

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

25. Claims 92, 106, and 111 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Farr et al. (US005811231A).

26. Farr et al. describes a method for determining and characterizing the toxicity (predict) of a compound in terms of the damage it causes within the cell (column 5, lines 49-61 and columns 24-32). The test compounds are listed in Table 3 (column 30). The method of Farr et al. is directed to cells from mammalian liver such as HepG2 (hepatotoxicity) (column 6, lines 11-24). Farr et al. discloses at least 50 different mammalian stress genes have already been isolated and characterized. These genes are induced by a variety of chemical and physical stresses or cellular damage (column 5, lines 23-27). The method of Farr et al. comprises exposing cells to a compound and creating an inducing profile (expression profile) (column 53, lines 4-7). The method of Farr et al. is directed to the “at least 10 genes” discussed below, as in instant claims 92 and 111, (a).

27. Farr et al. discloses a database (Tables 1 and 2) of gene expression profiles comprising the GADD153, GADD45, HSP70, UGT, DNA pol, EH, CYP2E1, ALDH1 and ALDH2, IL-3, and IL-6 genes (claims 9 and 10). The genes disclosed by Farr et al. represents the at least 10 genes in Tables 3A-3S of the instant Application which are identified by the GLGC ID NOs: 351 (GADD45), 488 (CYP2E1), 1475 (HSP70), 1598 (GADD153), 2744 (UGT), 6615 (alcohol dehydrogenase), 14103 (EH), 14465 (DNA pol), and 20799 (IL3 and IL6). The method comprises comparing the expression profile to the at least 10 genes determined in claims 17-32 to the expression profiles in the databases comprising the above identified genes (claim 33) as directed to the exposed toxin, as in instant claims 92 and 111, (b).

28. Farr et al. discloses exposure to the CCl₄ (carbon tetrachloride) stress toxin (column 4, line 17), as in instant claim 106.

CLAIM REJECTIONS - 35 USC § 103

29. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

30. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

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evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

31. Claims 92, 97-101, 111, and 116-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farr et al. (US005811231A).

32. Farr et al. discloses the limitations to claims 92 and 111 as discussed above.

33. However, Farr et al. does not describe the limitations of claims 97-101 and 116-120 as directed to the specified number of genes that are compared to the database.

34. Farr et al. discloses at least 50 different mammalian stress genes have already been isolated and characterized. These genes are induced by a variety of chemical and physical stresses or cellular damage (column 5, lines 23-27), as in instant claims 97-101 and 116-120.

35. It is noted that Farr et al. describes the database comprising the “at least 10 genes” as required by claims 92 and 111. Further, it has been reasonably construed that a search (comparison) using any of the “at least 50 different mammalian stress genes” against the Farr et al. database would result in matches for the “at least 10 genes” identified above if present. The genes beyond the “at least 10 genes” would result in no matches if not present in the database.

36. Farr et al. describes an improvement that has the time and cost-saving features based on the use of eukaryotic cells (column 2, lines 47-49) for predicting the toxicity of a compound. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated by the improvement described by Farr et al. and compare the disclosed “at least 50 different

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mammalian stress genes” to the database for predicting the toxicity of a compound. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the method of Farr et al. for predicting the toxicity of a compound.

37. Claims 92, 107, 111, and 126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farr et al. (US005811231A) in combination with Lashkari et al. (1997).

38. Farr et al. describes the limitations of claims 92 and 111 as discussed above.

39. However, Farr et al. does not describe the limitation of microarray recited in claims 107 and 126.

40. Lashkari et al. describes genome arrays provide for a robust, fully automated approach toward examining genome structure and gene function (page 13062, column 2, last paragraph). Figure 1 illustrates the use of microarray of Lashkari et al. for generating gene expression profiles, as in instant claims 107 and 126.

41. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated by the improvement described by Lashkari et al. for a robust, fully automated approach toward examining genome structure and gene function to apply such improvement to the method of Farr et al. for predicting the toxicity of a compound by gene function. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the method for predicting the toxicity of a compound using a microarray as described by Farr et al. and Lashkari et al.

CONCLUSION

42. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. The USPTO's official fax number is (571) 273-8300.

43. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

44. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

45. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

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46. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718.

C. Dune Ly / *CAL*
5/31/05

Ardin H. Marschel
ARDIN H. MARSCHEL
PRIMARY EXAMINER 5/31/05